Pergamon

Tetrahedron Letters 42 (2001) 9127–9130

TETRAHEDRON LETTERS

Fluorinated resveratrol and pterostilbene

Said Eddarir,[a,b] Zouanate Abdelhadi[b] and Christian Rolando[a,*]

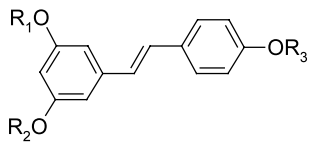
[a]*Université des Sciences et Technologies de Lille, UPRESA CNRS 8009, Chimie Organique et Macromoléculaire, 59655 Villeneuve d'Ascq Cedex, France*

[b]*Université Cadi Ayyad, Faculté des Sciences et Technique Guéliz, BP 618 Marrakech, Maroc*

Received 1 August 2001; accepted 30 August 2001

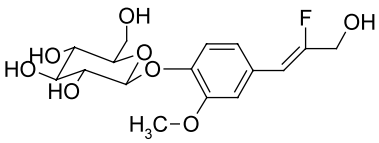
Abstract—A general method for the synthesis of polyhydroxylated stilbene monofluorinated on the central double bond based on the Suzuki reaction between a bromofluoroolefin and a phenylboronic acid is described. Synthesis of fluorinated analogues of resveratrol and pterostilbene was achieved using this strategy.

Resveratrol, and more generally polyhydroxylated stilbenes are natural compounds which exhibit many biological properties. As they are widely distributed in plants, especially in grape they are very often found in human diet. Since the pioneering discovery of their anti-carcinogenic[1] and anti-oestrogenic[2] properties a great number of studies has been devoted to understand their biological effects.[3]

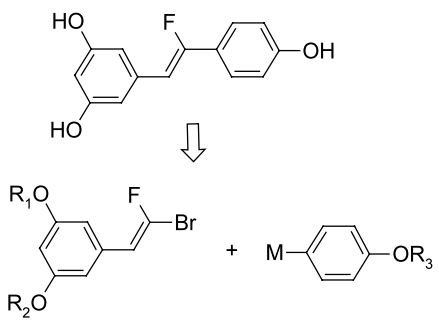


Resveratrol:
$R_1=R_2=R_3=H$;
Piceid: $R_1=R_3=H$;
R_2=β-D-Glucose
Pterostilbene:
$R_1=R_2=Me$; $R_3=H$;

In grapevines polyhydroxylated stilbenes are strong protectors of the plant against the attack by pathogen fungi like *Botrytis* cinerea.[4] Pterostilbene has been shown to be the more efficient phytoalexin and this activity is well correlated with its strong inhibition of *Botrytis* cinerea laccase.[5] Most of the time, the introduction of a fluorine atom on a key double bond of a natural compound leads to a strong inhibitor of the enzymatic system responsible for its metabolization. For example fluoroconiferylic alcohol, injected as its glycoside, fluoroconiferine, which is the transported form in the plant, is a strong inhibitor of lignification.[6]



So we decided to synthesize resveratrol fluorinated on the stilbene double bond in order to test its biological activity against oxidation enzymes. Most of the previously described syntheses of resveratrol and analogues rely on the Wittig or Wittig–Horner reactions.[7–14] The coupling of a benzyl anion with a benzaldehyde followed by the dehydration of the alcohol may equally lead to the central double bond.[15] The hydroxyl groups are protected on both precursors as methyl ethers, which are cleaved under harsh acidic (pyridinium hydrochloride at reflux,[7–9] BBr_3,[11,12] MeMgI at 100–160°C[15]) or basic (lithium diphenylphosphide)[11,12] conditions. More recently a synthesis of piceid using *ter*-butyldimethylsilyl ethers as protecting group for the resorcinol ring has been described, but the phenol group was still protected by a methyl group, which required the use of sodium ethanethiolate in DMF for cleavage.[13,14] In our target molecule the fluorinated double bond is by far too sensitive to either such basic or acidic conditions. So we decided to use a methoxymethyl ether as a protecting group for its ease of deprotection in slightly acidic conditions, as most phenols are very unstable in basic medium and as methoxymethyl ethers has been reported to be stable under organometallic reaction conditions.[16,17]

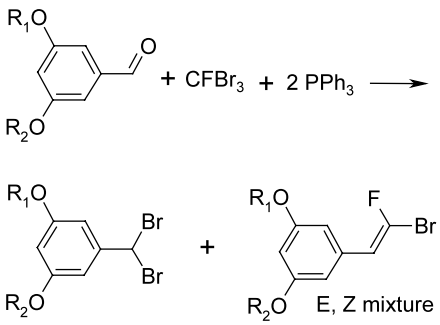


* Corresponding author. Tel.: +33-3 20 43 49 77; fax:+33-3 20 33 61 36; e-mail: christian.roland@univ-lille1.fr

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01800-7

The organometallic synthesis of phenols is well documented.[18] The total synthesis of Combrestatin A-4 illustrates the scope of this approach.[19] Furthermore recently a series of cross coupling reactions of resorcinol has been described.[20] So we chose to construct the fluorinated double bond by coupling the required bromofluoroolefin with an organometallic reagent using palladium catalysis. We previously described such a strategy for the synthesis of fluoroolefins, dienes and enynes based on the Stille reaction using organotin reagent.[21–23] Recently, McCarthy extended this synthesis to the Suzuki reaction.[24–27] The palladium-catalyzed coupling reaction between either a fluorinated organometallic and an aromatic or a vinylic halide, or between an organometallic and a fluorinated iodo, bromo or chloroolefin is quite general, working on a wide scope of substrates, even on polyfluorinated compounds.[28–31] In order to avoid the introduction of tin in compounds dedicated to biochemical experiments we decided to use a phenylboronic acid for the coupling step.

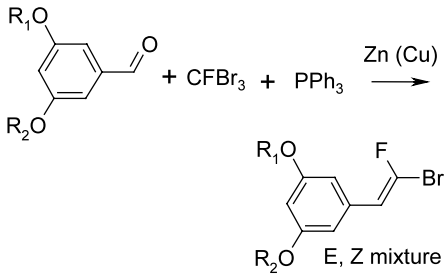
There are three main synthetic pathways leading to the required bromofluoroolefins: (i) transformation of the corresponding fluoroacrylate by bromine addition followed by dehydrogenative decarboxylation;[21–23] (ii) condensation of $LiCFBr_2$ on an aldehyde followed by water elimination;[32,33] (iii) reaction of fluorotribromethane with aldehyde in presence of a tertiary phosphine according to the procedure developed for the synthesis of dibromoolefins by Corey[34] and adapted to bromofluoroolefins by Burton.[35–37] We chose this later strategy, as it is compatible with functionalized molecules like carbohydrates[38] or nucleotides.[39] Happily this procedure appeared to be compatible with the methoxymethyl ether protecting group. However, using 2 equiv. of triphenylphosphine we always got a 50/50 mixture between the gemdibromo compound derived from the aldehyde (reported here for the first time in this reaction to the best of our knowledge) and the E/Z bromofluorolefin mixture.



This reaction can be readily explained from the stoichiometry of the reaction leading to the intermediate phosphorane.

$$CFBr_3+2PPh_3 \rightarrow Ph_3PCFBr+Ph_3PBr_2$$

As the gemdibromo compound and the bromofluoroolefins were very difficult to isolate by chromatography, we chose to use alternative conditions using one equivalent of triphenylphosphine in the presence of zinc dust. In our hands, only zinc activated by cupric sulfate[40] gave good results, which are reported in Table 1.



4-(Methoxymethyl)oxyphenylboronic acid was prepared according to the procedure described by Hibino and co-workers using triisopropyl borate as the trapping reagent[17] whereas 4-methoxy or 3,5-dimethoxyphenylboronic acids were synthesized using standard procedures. Among the various conditions used for the Suzuki reaction,[41,42] McCarthy and co-workers used $Pd(PPh_3)_4$ along with sodium carbonate in benzene, ethanol–water for the coupling of bromofluoroolefin with phenylboronic acids.[24–27] At the sight of: (i) the acceleration of the Suzuki reaction in presence of fluoride ions,[43] when fluoroarylborates are used;[44] (ii) the ease of transformation of boric acid to fluoroborate by potassium hydrogenfluoride;[45] (iii) the improved yield using phase transfer catalyst[46] we chose to use the $PdCl_2(PPh_3)_2/PPh_3$ system in presence of the non-basic reagent n-Bu_4N^+, HF_2^- in THF,[47] we used previously for the Stille reaction.[48] After 4 h at reflux, TLC indicated a near complete transformation of the starting bromofluoroolefin.

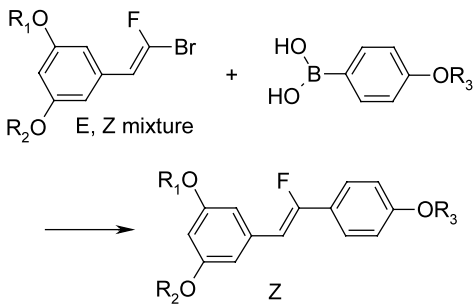
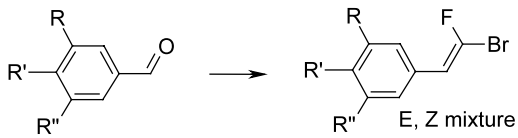


Table 1. Synthesis of protected β,β-bromofluoro-hydroxystyrenes

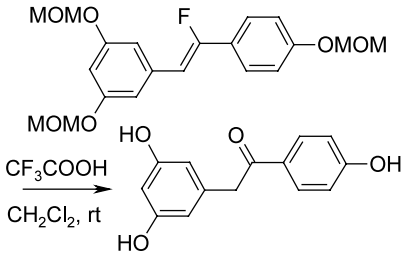


R (*meta*)	R′ (*para*)	R″ (*meta*)	Isolated yield (%)
MeO	H	MeO	55
$CH_3C(O)O$	H	$CH_3C(O)O$	41
CH_3OCH_2O	H	CH_3OCH_2O	46
H	MeO	H	52
H	CH_3OCH_2O	H	48
H	NO_2	H	56

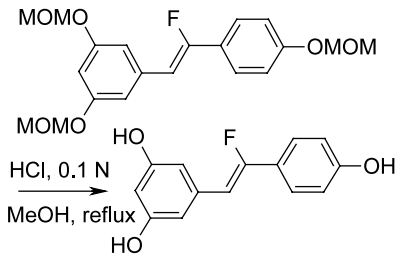
Table 2. Synthesized polyhydroxylated fluorostilbenes

$R_1=R_2$	R_3	Suzuki coupling yield (%)	Deprotection isolated yield (%)
Me	Me	86	–
Me	CH_3OCH_2O	83	76
CH_3OCH_2O	CH_3OCH_2O	71	73
CH_3OCH_2O	Me	84	80

Our first attempt to deprotect the fluororesveratrol blocked by three MOM groups using trifluoroacetic acid in dichloromethane[49] at room temperature led to the formation of the ketone resulting from the hydrolysis of the fluorinated enol. The ketone was identified by its ESI–MS/MS spectrum, which exhibits peaks at m/z 121 and 151 corresponding to the acylium ion and the benzyl cation.

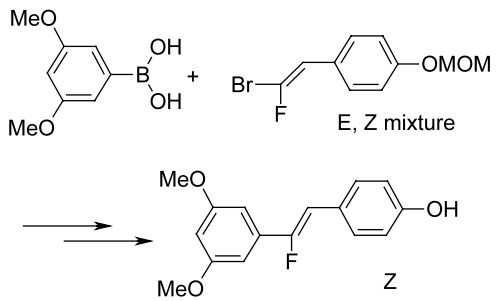


We were delighted that using milder conditions, aqueous HCl 0.1N in MeOH at reflux, the three MOM groups could be cleaved without hydrolysis of the carbon–fluorine bond. After optimization of the reaction time (36 h) a near quantitative yield of fluoresveratrol has been achieved.[50]



A series of analogues including fluoropterostilbene has been synthesized in the same way. Results are summarized in Table 2.

The synthesis was also extended to the family of molecules with the fluorine located on the resorcinol moiety as exemplified by the synthesis of the isomeric fluoropterostilbene (coupling and deprotection yields: 85, 78%, respectively).



In summary, the synthesis of fluorinated analogues of resveratrol and pterostilbene was achieved based on the Suzuki reaction between a bromofluoroolefin and a phenylboronic acid. The choice of the protecting group was rather critical due to the sensitivity of the fluoroolefins to hydrolysis. The methoxymethyl protecting group appeared to be both stable under coupling conditions and easily cleaved under mild acidic conditions, opening the way to a general synthesis of polyhydroxylated stilbenes monofluorinated on the central double bond. The synthesized fluorinated compounds are currently tested in various in vitro biological experiments.

Acknowledgements

This work was supported by the European Community (European Contract QLK1-CT-199-00505 POLYBIND) and the Conseil Régional Nord, Pas-de-Calais. S.E. thanks the Université Cadi Ayyad, Faculté des Sciences et Technique Guéliz for a sabbatical leave. Professor Florence Charbonnier, Université Joseph Fourier, Grenoble, France, is gratefully thanked for helpful discussions on zinc activation.

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50. A dry flask with a reflux condenser was flushed with argon prior to adding 3,5-di-[(methoxymethyl)oxy]-benzaldehyde (335 mg, 1.48 mmol), fluorotribromethane (1.5 equiv., 603 mg, 2.22 mmol), triphenylphosphine (1 equiv., 388 mg, 1.48 mmol) and 5 ml of freshly distilled THF. Freshly prepared Zn(Cu) (1.5 equiv., 144 mg, 2.22 mmol) was then added and the flask was heated at reflux during 4 h. After cooling, the organic phase was diluted with diethyl ether then washed with water and dried over $MgSO_4$. Column chromatography on silica gel (eluent ethyl acetate, petroleum ether 10/90) afforded 221 mg (yield 46%) of the 3,5-di-[(methoxymethyl)oxy]-β-bromo-β-fluorostyrene as an E/Z mixture (57/43).
3,5-di-[(Methoxymethyl)oxy]-β-bromo-β-fluorostyrene (E/Z mixture, 210 mg, 0.65 mmol), 4-(methoxymethyl)-oxyphenylboronic acid (1.3 equiv., 155 mg, 0.85 mmol), dichloro-bis-(triphenylphosphine)-palladium(II) (23 mg, 5%), triphenylphosphine (17 mg, 10%), tetrabutylammonium fluoride trihydrate (3 equiv., 618 mg, 1.96 mmol) and 5 ml of freshly distilled THF were added in a flask fitted with a reflux condenser. After flushing with argon the flask was heated at reflux 5 h. The same extraction procedure as above (except the eluent ethyl acetate, petroleum ether 15/85) gave 182 mg (yield 71%) of the fully protected tris-(MOM)-fluororesveratrol, mostly as the Z isomer (>95%).
A mixture of the fully protected tris-(MOM)-fluororesveratrol (60 mg, 0.16 mmol), MeOH (7 ml) aqueous HCl 0.1N (8 ml) was heated at reflux under argon during 36 h. After cooling the aqueous methanol solution was extracted with ethyl acetate. The organic phase was then washed with water and dried over $MgSO_4$. Column chromatography on silica gel (eluent ethyl acetate, petroleum ether 50/50) afforded 29 mg (yield 73%) of fluororesveratrol mostly as the Z isomer (>95%).
Mp: 200.5°C; MS (ESI$^+$): m/z 247 $[M+H]^+$; ^{1}H NMR (acetone-d_6, 300 MHz): δ 6.25 (1H, d, $^3J_{HF}=39.3$ Hz), 6.30 (1H, t, $J=2.3$ Hz), 6.65 (2H, d, $J=2.3$ Hz), 6.90 (2H, $J=8.6$ Hz), 7.55 (2H, d, $J=8.6$ Hz).